

Antitumor activity of combination 5,10-methylenetetrahydrofolate, 5-fluorouracil, and anti-vascular endothelial growth factor against human colorectal HT-29 tumors in nude mice.

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Background: Folinic acid (leucovorin) has been used as the standard combination therapy as a modulator of 5-fluorouracil (5-FU) for cancer treatment. However, leucovorin is inactive directly and must undergo several metabolic transformations to its active metabolite 5,10-methylenetetrahydrofolate (CoFactor) to be effective. In contrast, CoFactor supplies 5,10-methylenetetrahydrofolate directly and has demonstrated enhancement of the antitumor effects of 5-FU in Phase I/II human clinical trials for colorectal and breast cancer. To determine if the antitumor activity of CoFactor/5-FU could be enhanced further, we examined its use in combination with a recombinant antibody specific for vascular endothelial growth factor (α VEGF), an inhibitor of angiogenesis, against human colorectal HT-29 tumors in nude mice. **Methods:** 6-8 week old nude mice (nu/nu) were inoculated subcutaneously with 2×10^6 HT-29 cells. When tumors reached 0.1 to 0.3 cm³ in volume, mice were treated with various combinations of 5-FU, CoFactor, leucovorin, and α VEGF administered by intraperitoneal injection. All drugs were dosed daily (0.6 mg/mouse/drug) for five consecutive days with the exception of α VEGF, dosed once (100 μ g/mouse) on day 1. In addition, CoFactor or leucovorin were injected 20 minutes prior to 5-FU injection. Tumor volumes were calculated every 2 to 3 days. **Results:** One month following treatment, we observed smaller mean tumor volumes in mice treated with combination CoFactor/ α VEGF/5-FU ($0.48 \text{ cm}^3 \pm 0.1$, n=8, mean \pm SEM) than mice treated with either 5-FU alone ($0.75 \text{ cm}^3 \pm 0.1$), CoFactor/FU ($0.52 \text{ cm}^3 \pm 0.08$), or leucovorin/5-FU ($0.71 \text{ cm}^3 \pm 0.09$). Furthermore, there was greater survival of mice treated with CoFactor/5-FU either with or without α VEGF (57% and 88%, respectively) compared to mice treated with only 5-FU (25%). **Conclusions:** This study suggests combination CoFactor/ α VEGF/5-FU treatment might have utility as a colorectal tumor therapy with greater antitumor activity than standard 5-FU therapies.